Dopaminergic toxicity of 1-methyl-4-phenylpyridinium (MPP+): Model for Parkinson’s disease

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Parkinson's disease (PD) is among the most common neurodegenerative diseases. Approximately 60,000 Americans are diagnosed with this disease every year. The cause or cure for PD remains unknown. MPP+ is a dopaminergic neurotoxin that induces symptoms similar to PD and commonly used as a good model to study the molecular causes of PD. The specific dopaminergic toxicity of MPP+ is proposed to be due to the uptake through dopamine transporter (DAT) followed by the inhibition of complex I of the electron transport chain leading to cellular energy starvation. However, this proposal has not been conclusively established. We investigated the mechanism of MPP+ toxicity using MN9D (neuronal) and HepG2 (non-neuronal) cell models. Our studies show that both cells take-up substantial levels of MPP+ under similar experimental conditions, while only MN9D cells are susceptible to MPP+toxicity. MPP+ toxicity is independent of DAT in MN9D cells. Extracellular Ca2+decreases MPP+ uptake into MN9D cells, but has no effect on the toxicity. Voltage-gated Ca2+ channel blockers decrease the MPP+ uptake into MN9D cells, but again do not protect the MN9D cell from MPP+ toxicity. These and other findings suggest a novel mechanism in which MPP+ perturb intracellular Ca2+ leading to neuronal cell death. The understanding of the causes of PD at the molecular level could lead to the development of therapeutic and preventive measures.